47. (Amended) A sperm cell obtained from a male [non-human] transgenic [mammal] mouse, wherein said [mammal] mouse comprises an isolated DNAc molecule, said DNAc molecule comprising a promoter P and an L1 cassette sequence comprising a core L1 retrotransposon element, wherein said core L1 retrotransposon element comprises a 5' UTR, ORF1, ORF2 comprising EN and RT domains, a 3' UTR, a poly A signal, and a vector sequence comprising at least one origin of DNA replication and a DNA sequence encoding at least one selectable marker protein.

49. (Amended) A [non-human] transgenic [mammal] mouse obtained by fertilization of an egg with the sperm cell of claim 47, wherein said egg is obtained from a female [non-human mammal] of the same species as said [non-human] transgenic [mammal] mouse from which said sperm is obtained.

Remarks

In compliance with the Examiner's comments, a new oath or declaration will be filed in the application, identifying this application by application number and filing date, pursuant to and referring to the Preliminary Amendment filed on September 1, 2000. (The Applicants believe that the fault the Examiner has found with the oath/declaration may be pursuant to 37 C.F.R. 1.67 (b), not 37 C.F.R. 1.67 (a) as cited by the Examiner. If the Applicants are mistaken, the Examiner is respectfully invited to address this with the undersigned.)

The invention relates to a transgenic mouse and a mouse sperm cell comprising a DNAc molecule. The DNAc molecule further comprises a promoter P, an L1 cassette, and non-L1 DNA.

By way of the present Amendment, Applicants have canceled claims 35, 45, and 48, without prejudice, and amended claims 34, 36-44, 46, 47, and 49. Thus claims 34, 36-44, 46, 47, and 49 are pending in the present application. A marked up copy and clean copy of the amended claims presently pending in the application is included herewith.

As described in detail below, claims 34, 36-44, 46, 47, and 49 have been amended herein to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Support for these amendments is found in the specification as filed as more fully set forth below. Thus, no new matter has been introduced by way of these amendments.

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Rejection of Claims 34, 36-44, 46, 47, and 49 under 35 U.S.C. § 112, First Paragraph

The rejections cited in the Office Action that pertain to claims 35, 45, and 48 are not addressed herein as they are moot in view of the cancellation of these claims. Claims 34, 36-44, 46, 47, and 49 are pending in the application, and have been rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention. The Examiner contends that the specification fails to provide an enabling disclosure because the phenotype of the transgenic mammal is unpredictable.

Applicants, while not necessarily agreeing with the Examiner's reasoning but in a good faith effort to expedite prosecution of this application, have amended claims 34, 36-44, 46, 47, and 49 to recite a transgenic mouse rather than a transgenic mammal. As pointed out by the Examiner on page 4 of the Office Action (paper No. 5), "gene-transfer techniques are well-developed for a number of species, especially the mouse...". Further, beginning on page 38, line 17 of the specification, methods for the generation of transgenic animals, especially mice, are presented in the text and by reference. The Examiner points out that the genetic elements required for expression in one animal may be different than the genetic elements required for expression in another animal, and that physiological differences between species can lead to unpredictable phenotypes in transgenic animals expressing the same nucleic acid construct. By way of the present Amendment, the scope of the claims clearly recites the invention as it pertains to a transgenic mouse. The specification clearly teaches the generation of a transgenic mouse. Applicants respectfully submit that the present Amendment overcomes the Examiner's rejection of claims 34, 36-44, 46, 47, and 49 and Applicants respectfully request that the Examiner withdraw the rejection.

Claims 34, 36-44, 46, 47, and 49 have also been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention. The Examiner contends that the specification does not teach how to use a transgenic animal that does not exhibit a specific transgene-dependent phenotype, and that the claims encompass a transgenic animal exhibiting an undisclosed and unspecified transgene-dependent phenotype, but the specification does not teach how to use the transgenic animal.

Applicants respectfully traverse this rejection and argue that the specification in fact teaches how to use the claimed transgenic animal, and that a transgenic phenotype is disclosed and specified.

Applicants respectfully point out that retrotransposons, by their very nature, integrate randomly into the genome. The literature describes disease states induced by the random integration of retrotransposons into the genome, and a partial list is given in the specification (page 3, beginning at line 7). As described in the specification (page 2, line 14) many naturally occurring retrotransposons are truncated, and therefore incapable of integrating into the host genome. The present invention discloses an isolated DNAc molecule comprising the elements of a retrotransposon capable of integration in the genome. The disclosed retrotransposon is capable of random integration, or directed insertional mutagenesis. Methods to affect directed insertional mutagenesis are disclosed throughout the specification. A partial list of examples can be found at page 23, beginning at line 22, page 28, beginning at line 15, and page 33, beginning at line 10.

In either embodiment of the disclosed invention, whether the isolated DNAc molecule integrates into the host genome randomly or in a directed, sequence-specific fashion, the phenotype of the resulting transgenic animal is readily apparent as disclosed in the specification. As an example, on page 34, beginning at line 15, the specification clearly describes a phenotype resulting from the sequence-specific integration of a retrotransposon cassette. In this example, the animal is treated with a retrotransposon cassette comprising the wild type, or active portion, of the cystic fibrosis transmembrane regulator (CFTR) gene. The phenotype would be alleviation of the symptoms of cystic fibrosis in an animal exhibiting such symptoms as a result of having a mutated CFTR gene.

Applicants respectfully direct the Examiner's attention to page 6, beginning at line 18, and page 20, beginning at line 6 of the specification for more examples of a disclosed and specified phenotype in the transgenic animal of the invention. In this example, a genetic defect is corrected in an animal of the invention specifically by way of the non-L1 DNA of the invention expressing a protein for the correction of the genetic defect. Contemplated proteins include adenosine deaminase, hypoxanthine guanine phosphoribyl transferase, p53, p21, p16, retinoblastoma, Wilm's tumor, interleukins, β globin, a blood clotting protein, an enzyme, a tumor suppressor protein, mutated genes resulting in lysosomal storage and metabolic diseases,

therapeutic peptides, and cytokines. Further contemplated is CFTR protein, already discussed above. In theses numerous examples, the disclosed and specified transgene dependent phenotype is alleviation of the disease state resulting from the genetic defect.

It is respectfully submitted that the specification as filed discloses many instances of a disclosed transgenic-dependent phenotype. Therefore, the rejection under 35 U.S.C. § 112, first paragraph, should be reconsidered and withdrawn.

The Examiner has also rejected claims 34, 36-44, 46, 47, and 49 pursuant to 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not teach how to use the claimed transgenic animals.

Applicants respectfully direct the Examiner's attention to multiple sections of the specification, as detailed below, which recite many examples teaching how to use the claimed transgenic animals.

Beginning on page 24, line 3, the specification teaches how to use the transgenic mammal of the present invention to isolate and clone specific genes from the transgenic animal's chromosome. Briefly, a marker gene in the 3' UTR region of the retrotransposon can be used to easily identify host genomic DNA flanking the site of retrotransposon insertion, and with the disclosed inclusion of a prokaryotic origin of replication, the specification teaches how to use the transgenic mammal as a way to facilitate one-step cloning.

Ways to use the present invention are also detailed on page 24, line 19 of the specification. Briefly, the specification teaches how to use a transgenic animal with the promoter and start codon of the marker gene eliminated, thereby generating a fusion protein with an endogenous transgenic animal protein. The specification therefore teaches how to use the present invention as a "gene trap". This technology can be slightly modified, as detailed beginning on page 24, line 24 to effect knockout of a gene, promoter or enhancer in the transgenic mammal using antisense technology.

The specification further teaches how to use the "gene trap" or "promoter trap" on page 28, line 4 of the specification. In this contemplated embodiment, the technology outlined earlier can be used to provide mutations in somatic cells, and may further be used to identify and mutate genes providing tumor resistance or susceptibility.

Applicant's respectfully direct the Examiner's attention to page 36, line 16 of the specification, where a method to use the transgenic mammal of the present invention is detailed.

Briefly, the specification teaches a method of identifying and cloning genes that were previously unknown or unclonable by virtue of the ability to identify and isolate a sequence comprising the tag of the DNAc molecule.

Given these examples, Applicants respectfully submit that the specification provides many ways to use an animal exhibiting a transgenic-dependent phenotype, and the Examiner's rejection of claims 34, 36-44, 46, 47, and 49 under 35 U.S.C. § 112, first paragraph, respectfully, should be withdrawn.

The Examiner has also rejected claims 34, 36-44, 46, 47, and 49 under 35 U.S.C. § 112, first paragraph on the grounds that the generation of transgenic animals is unpredictable.

Applicants have amended claims 34, 36-44, 46, 47, and 49, and cancelled claims 35, 45, and 48, to more clearly recite what the Applicants regard as their invention. Further, the amendments as filed herewith clarify the claims to recite a transgenic mouse, which both Applicants and Examiner agree is the best characterized and most well known species for the generation of transgenic animals.

The Examiner, to add credence to her point that the generation of transgenic animals in unpredictable, cited several references. Wall (1996) points to the unpredictability of generating transgenic livestock. This point in inapplicable in view of the fact that the claims recite on a mouse. In addition, Wall points out that a great majority of the papers published on transgenic animals have been directed towards mice (page 58, first paragraph), therefore indicating that mice are the most common, and therefore predictable species in which to generate transgenic mammals.

Additionally, the Examiner cited several references to point out that the species-specific requirements of transgene design are not clearly understood, and that the same construct, when expressed in different species, may result in different phenotypes. The Examiner cited Mullins et al., 1989 and Mullins et al., 1990, to show the species-specific differences in phenotypes resulting from the expression of the same gene in transgenic mice and transgenic rats. By way of the present Amendment, Applicants have specifically claimed transgenic mice, nullifying these two references as a point of argument.

The Examiner cites two articles (Taurog et al., 1988, and Hammer et al., 1990) to further emphasize that the transgene-dependent phenotype may differ depending on the species in which the same transgene is expressed. Taurog (1988) successfully generated transgenic mice

expressing HLA-B27, and these mice expressed a functional HLA-B27 gene product, (page 4020, first paragraph) as assayed by Southern blot and FACS analysis. Hammer (1990) generated transgenic rats expressing HLA-B27 for a different purpose. As stated in Hammer (page 1099, second column, second paragraph), the choice of rats was due to their well known and increased susceptibility to arthritic disorders. Both Taurog and Hammer were able to achieve successful and predictable expression of a transgenic phenotype, and as they were investigating different effects of the expression of the same gene, it is only logical that they should use different animals, with different characteristic susceptibilities.

Summary

Applicants respectfully submit that each rejection of the claims of the present application has been overcome or is now inapplicable, and that each of the claims 34, 36-44, 46, 47, and 49, is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

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April 15, 2002
(Date)

By: _____

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Enclosures: Marked up copy of the claims
Clean copy of the claims
Petition for Extension of Time with Fee Authorization

MARKED UP COPY OF THE CLAIMS

34. (Amended) A [non-human] transgenic [mammal] mouse comprising an isolated DNAc molecule, wherein said DNAc molecule comprises a promoter P and an L1 cassette sequence comprising a core L1 retrotransposon element.

36. (Amended) The [non-human] transgenic [mammal] mouse of claim [35] 34, wherein said core L1 retrotransposon element comprises a 5' UTR, ORF1, ORF2 comprising EN and RT domains, a 3' UTR, a poly A signal, and a vector sequence comprising at least one origin of DNA replication and a DNA sequence encoding at least one selectable marker protein.

37. (Amended) The [non-human] transgenic [mammal] mouse of claim [35] 34, wherein said promoter P is an RNA pol III promoter or an RNA pol II promoter, said RNA pol II promoter being selected from the group consisting of a constitutive promoter, an inducible promoter, a tissue-specific promoter and a viral promoter.

38. (Amended) The [non-human] transgenic [mammal] mouse of claim 36, wherein said origin of DNA replication is a eukaryotic origin of DNA replication.

39. (Amended) The [non-human] transgenic [mammal] mouse of claim 38, wherein said isolated DNAc molecule further comprises a prokaryotic origin of DNA replication.

40. (Amended) The [non-human] transgenic [mammal] mouse of claim 36, wherein said selectable marker protein is a first marker protein selected from the group consisting of neomycin resistance protein, green fluorescent protein, β-galactosidase, and a prokaryotic antibiotic resistance protein.

41. (Amended) The [non-human] transgenic [mammal] mouse of claim 36, wherein said isolated DNAc molecule further comprises a fragment of non-L1 DNA and a promoter P' for expression of said non-L1 DNA, wherein said non-L1 DNA and promoter P' are positioned within said 3' UTR or between said 3' UTR and said poly A signal.

42. (Amended) The [non-human] transgenic [mammal] mouse of claim of claim 41, wherein said non-L1 DNA comprises DNA encoding a second marker protein.

43. (Amended) The [non-human] transgenic [mammal] mouse of claim 42, wherein said second marker protein is selected from the group consisting of neomycin resistance protein, green fluorescent protein, β-galactosidase, herpes simplex virus thymidine kinase, and a eukaryotic cell surface protein.

44. (Amended) A sperm cell obtained from a male [non-human] transgenic [mammal] mouse, wherein said [mammal] mouse comprises an isolated DNAc molecule, wherein said DNAc molecule comprises a promoter P and an L1 cassette sequence comprising a core L1 retrotransposon element.

46. (Amended) A [non-human] transgenic [mammal] mouse obtained by fertilization of an egg with the sperm of claim 44, wherein said egg is obtained from a female [non-human transgenic mammal] of the same species as said [non-human] transgenic [mammal] mouse from which said sperm is obtained.

47. (Amended) A sperm cell obtained from a male [non-human] transgenic [mammal] mouse, wherein said [mammal] mouse comprises an isolated DNAc molecule, said DNAc molecule comprising a promoter P and an L1 cassette sequence comprising a core L1 retrotransposon element, wherein said core L1 retrotransposon element comprises a 5' UTR, ORF1, ORF2 comprising EN and RT domains, a 3' UTR, a poly A signal, and a vector sequence comprising at least one origin of DNA replication and a DNA sequence encoding at least one selectable marker protein.

49. (Amended) A [non-human] transgenic [mammal] mouse obtained by fertilization of an egg with the sperm cell of claim 47, wherein said egg is obtained from a female [non-human mammal] of the same species as said [non-human] transgenic [mammal] mouse from which said sperm is obtained.